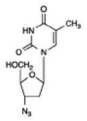
ZIDOVUDINE - zidovudine syrup
Cipla Ltd.

WARNING
ZIDOVUDINE HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIDOVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

Zidovudine (formerly called azidothymidine [AZT]) is a pyrimidine nucleoside analogue active against HIV.
Zidovudine oral solution is for oral administration. Each teaspoonful (5 mL) of Zidovudine Syrup contains 50 mg of zidovudine and the inactive ingredients are sodium benzoate 0.2% (added as a preservative), citric acid, flavors, glycerin, and sucrose.
The chemical name of zidovudine is 3#-azido-3#-deoxythymidine; it has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

MICROBIOLOGY

Mechanism of Action

Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5#-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity

The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM, respectively. HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.011 μM (range: 0.005 to 0.110 μM) from Virco (n = 93 baseline samples from COLA40263) and 0.02 μM (0.01 to 0.03 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and against HIV-2 isolates from 0.00049 to 0.004 μM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Resistance

Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.
Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-Resistance

In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multi-drug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to

didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Adults

The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. Binding to plasma protein is low. Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is 3#-azido-3#-deoxy-5#-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration. A second metabolite, 3#-amino-3#-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC. Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

Table 1. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients

Parameter	Mean ± SD (except where noted)
Oral bioavailability (%)	64 ± 10 (n = 5)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 8)
Plasma protein binding (%)	<38
CSF:plasma ratio*	0.6 [0.04 to 2.62] (n = 39)
Systemic clearance (L/hr/kg)	1.6 ± 0.6 (n = 6)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 9)
Elimination half-life (hr)†	0.5 to 3 (n = 19)

*****Median [range].

†Approximate range.

Adults With Impaired Renal Function

Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) ≥15 mL/min.

Table 2. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment*

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•hr/mL)	1,400 ± 200	3,100 ± 300
Zidovudine half-life (hr)	1.0 ± 0.2	1.4 ± 0.1

*****Data are expressed as mean ± standard deviation.

The pharmacokinetics and tolerance of zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis **(SEE DOSAGE AND ADMINISTRATION: Dose Adjustment).**

Adults With Impaired Hepatic Function

Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment **(SEE DOSAGE AND ADMINISTRATION: Dose Adjustment).**

Pediatrics

Zidovudine pharmacokinetics has been evaluated in HIV-infected pediatric patients (Table 3).

Patients From 3 Months to 12 Years of Age

Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m^2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients,

the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV **(SEE DOSAGE AND ADMINISTRATION: Pediatric).**

Patients Younger Than 3 Months of Age

Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, **(SEE DOSAGE AND ADMINISTRATION: Neonatal Dosing).**

Table 3. Zidovudine Pharmacokinetic Parameters in Pediatric Patients*

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF:plasma ratio	no data	no data	0.68 [0.03 to 3.25]* (n = 38)
CL (L/hr/kg)	0.65 ± 0.29 (n = 18)	1.14 ± 0.24 (n = 16)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	3.1 ± 1.2 (n = 21)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

***Median [range]

Pregnancy

Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to those of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified **(SEE PRECAUTIONS).**

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum **(SEE PRECAUTIONS:Nursing Mother).**

Geriatric Patients

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gender

A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg zidovudine tablet.

Effect of Food on Absorption

Zidovudine may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food.

Drug Interactions

(SEE Table 4).and **(SEE PRECAUTIONS: Drug Interaction).**

Zidovudine Plus Lamivudine

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

Table 4. Effect of Co-administered Drugs on Zidovudine AUC* Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH CO-ADMINISTRATION OF THE FOLLOWING DRUGS.

Co-administered	Zidovudine		Zidovudine Concentrations		Concentration of Coadministered
Drug and Dose	Dose	n	AUC	Variability	Drug
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%*	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64%*	↔
Nelfinavir 750 mg q 8 hr x 7 To 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170%*	Not Assessed

Rifampin 600 mg daily x 14 days	200 mg q 8 hr x 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130%*	Not Assessed

↑ = Increase; ↓=Decrease; ↔ =no significant change; AUC= area under the concentration versus time curve. CI = confidence interval.
*****Estimated range of percent difference.

Ribavirin
In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were
co-administered as part of a multi-drug regimen to HIV/HCV co-infected patients **(SEE WARNINGS).**

INDICATIONS AND USAGE
Zidovudine in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Maternal-Fetal HIV Transmission
Zidovudine is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral Zidovudine beginning between 14 and 34 weeks of gestation, intravenous Zidovudine during labor, and administration of Zidovudine Syrup to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who have received Zidovudine for a prolonged period before pregnancy has not been evaluated. The safety of Zidovudine for the mother or fetus during the first trimester of pregnancy has not been assessed (see Description of Clinical Studies).

Description of Clinical Studies
Therapy with Zidovudine has been shown to prolong survival and decrease the incidence of opportunistic infections in patients with advanced HIV disease and to delay disease progression in asymptomatic HIV-infected patients.

Combination Therapy in Adults
Zidovudine in combination with other antiretroviral agents has been shown to be superior to monotherapy for one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4+ cell counts, and decreasing plasma HIV-1 RNA. The clinical efficacy of a combination regimen that includes Zidovudine was demonstrated in study ACTG320. This study was a multi-center, randomized, double-blind, placebo-controlled trial that compared Zidovudine 600 mg/day plus EPIVIR(300 mg/day to Zidovudine plus EPIVIR plus indinavir 800 mg t.i.d. The incidence of AIDS-defining events or death was lower in the triple-drug–containing arm compared to the 2-drug–containing arm (6.1% versus 10.9%, respectively). The complete prescribing information for each drug should be consulted before combination therapy that includes zidovudine is initiated.

Monotherapy in Adults
In controlled studies of treatment-naive patients conducted between 1986 and 1989, monotherapy with zidovudine, as compared to placebo, reduced the risk of HIV disease progression, as assessed using endpoints that included the occurrence of HIV-related illnesses, AIDS-defining events, or death. These studies enrolled patients with advanced disease (BW002), and asymptomatic or mildly symptomatic disease in patients with CD4+ cell counts between 200 and 500 cells/mm3 (ACTG016 and ACTG019). A survival benefit for monotherapy with Zidovudine was not demonstrated in the latter 2 studies. Subsequent studies showed that the clinical benefit of monotherapy with Zidovudine was time limited.

Pediatric Patients
ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of EPIVIR plus Zidovudine to didanosine monotherapy. A total of 471 symptomatic, HIV-infected therapy-naive pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), the mean baseline CD4+ cell count was 868 cells/mm^3, and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The median duration that patients remained on study was approximately 10 months. Results are summarized in Table 5.
Table 5. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)

Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Pregnant Women and Their Neonates
The utility of Zidovudine for the prevention of maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG076) conducted in HIV-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells/mm^3 (median in the treated group: 560 cells/mm^3) who had little or no previous exposure to Zidovudine. Oral Zidovudine was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of Zidovudine during labor and delivery. Following birth, neonates received Zidovudine oral solution for 6 weeks. The study showed a statistically significant difference in the incidence of HIV infection in the neonates (based on viral culture from peripheral blood) between the group receiving Zidovudine and the group receiving placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV infection was 7.8% in the group receiving zidovudine and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. Zidovudine was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

CONTRAINDICATIONS
Zidovudine oral solution is contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulation.

WARNINGS
COMBIVIR® and TRIZIVIR® are combination product tablets that contain zidovudine as one of their components. Zidovudine should not be administered concomitantly with COMBIVIR or TRIZIVIR.
The incidence of adverse reactions appears to increase with disease progression; patients should be monitored carefully, especially as disease progression occurs.

Bone Marrow Suppression
Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of Zidovudine, which was reversible in most instances after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of Zidovudine, and/or blood transfusions, has occurred during treatment with Zidovudine alone or in combination with other antiretrovirals.
Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with Zidovudine. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary **(SEE DOSAGE AND ADMINISTRATION).**

Myopathy
Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of Zidovudine.

Lactic Acidosis/Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretroviral. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering Zidovudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Zidovudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Use With Interferon- and Ribavirin-Based Regimens
In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co-administered with zidovudine in HIV/HCV co-infected patients **(SEE CLINICAL PHARMACOLOGY: Drug interaction). hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and Zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of Zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

PRECAUTIONS

General
Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function (CrCl<15 mL/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function, which may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Zidovudine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Fat Redistribution
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients
Zidovudine is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.
The safety and efficacy of Zidovudine in women, intravenous drug users, and racial minorities is not significantly different than that observed in white males.
Patients should be informed that the major toxicities of Zidovudine are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon alfa, which may exacerbate the toxicity of Zidovudine (see PRECAUTIONS: Drug Interactions). Patients should be informed that other adverse effects of Zidovudine include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with Zidovudine.
Zidovudine oral solution is for oral ingestion only. Patients should be told of the importance of taking Zidovudine exactly as prescribed. They should be told not to share medication and not to exceed the recommended dose. Patients should be told that the long-term effects of Zidovudine are unknown at this time.
Pregnant women considering the use of Zidovudine during pregnancy for prevention of HIV transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of in utero and infant exposure to Zidovudine are unknown, including the possible risk of cancer.
HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.
Patients should be advised that therapy with Zidovudine has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.
Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions
(SEE CLINICAL PHARMACOLOGY section table 4) for information on zidovudine concentrations when co-administered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

Antiretroviral Agents
Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro.

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of Zidovudine against HIV; concomitant use of such drugs should be avoided.

Doxorubicin
Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated in vitro (see CLINICAL PHARMACOLOGY for additional drug interactions).

Phenytoin
Phenytoin plasma levels have been reported to be low in some patients receiving Zidovudine, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Overlapping Toxicities
Co-administration of ganciclovir, interferon alfa, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.
In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.
In rats, 2 late appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.
At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.
Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.
It is not known how predictive the results of rodent carcinogenicity studies may be for humans.
Zidovudine was mutagenic in a 5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.
Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy
Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area under the curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.
Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, Impairment of Fertility).
A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of Zidovudine for the prevention of maternal-fetal HIV-transmission (see INDICATIONS AND USAGE: Description of Clinical Studies). Congenital abnormalities occurred with similar frequency between neonates born to mothers who received Zidovudine and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Antiretroviral Pregnancy Registry
To monitor maternal-fetal outcomes of pregnant women exposed to Zidovudine oral solution, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Zidovudine (**see Pediatric Use and INDICATIONS AND USAGE: Maternal-Fetal HIV Transmission).

Pediatric Use
Zidovudine has been studied in HIV-infected pediatric patients over 3 months of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. Zidovudine has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTION). (see DOSAGE AND ADMINISTRATION). (see INDICATION AND USAGE: Description of Clinical Studies). (see CLINICAL PHARMACOLOGY: Pharmacokinetic). .

Geriatric Use
Clinical studies of Zidovudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adults
The frequency and severity of adverse events associated with the use of Zidovudine are greater in patients with more advanced infection at the time of initiation of therapy.
Table 6 summarizes events reported at a statistically significant greater incidence for patients receiving Zidovudine in a monotherapy study:
Table 6. Percentage (%) of Patients with Adverse Events* in Asymptomatic HIV Infection (ACTG019)

Adverse Event	Zidovudine 500 mg/day (n = 453)	Placebo (n = 428)
Body as a whole		
Asthenia	8.6%*	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastrointestinal		
Anorexia	20.1%	10.5%
Constipation	6.4%*	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%

***Not statistically significant versus placebo

In addition to the adverse events listed in Table 6, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.
Selected laboratory abnormalities observed during a clinical study of monotherapy with Zidovudine
are shown in Table 7.
Table 7. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with Asymptomatic HIV Infection (ACTG019)

Adverse Event	Zidovudine 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1.1%	0.2%
Granulocytopenia (<750 cells/mm^3)	1.8%	1.6%
Thrombocytopenia (platelets<50,000/mm^3)	0%	0.5%
ALT (>5 x ULN)	3.1%	2.6%

AST (>5 x ULN)	0.9%	1.6%
Alkaline phosphatase (>5 x ULN)	0%	0%

Pediatrics

Study ACTG300

Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with Lamivudine 4mg/kg twice daily plus Zidovudine 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 8.

Table 8. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 9.

Table 9. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	Lamivudine plus Ziodvudine	Didanosine
Neutropenia (ANC<400 cells/mm^3)	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total amylase (>2.5 x ULN)	3%	3%

Additional adverse events reported in open-label studies in pediatric patients receiving zidovudine 180 mg/m^2 every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/ irritability, and weight loss.

The clinical adverse events reported among adult recipients of Ziodvudine may also occur in pediatric patients.

Use for the Prevention of Maternal-Fetal Transmission of HIV

In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of Ziodvudine for the prevention of maternal-fetal HIV transmission, Ziodvudine oral solution at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm^3). Anemia occurred in 22% of the neonates who received Ziodvudine and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving Ziodvudine compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with Ziodvudine Neutropenia was reported with similar frequency in the group that received Ziodvudine (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to Ziodvudine are unknown.

Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during use of Ziodvudine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to Ziodvudine, or a combination of these factors.

Body as a Whole

Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Cardiovascular

Cardiomyopathy, syncope.

Endocrine

Gynecomastia.

Eye

Macular edema.

Gastrointestinal

Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

General

Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic

Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas

Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal

Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

Nervous

Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory

Cough, dyspnea, rhinitis, sinusitis.

Skin

Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Special Senses

Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital

Urinary frequency, urinary hesitancy.

OVERDOSAGE

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

Adults

The recommended oral dose of zidovudine is 600 mg per day in divided doses in combination with other antiretroviral agents.

Pediatrics

The recommended dose in pediatric patients 6 weeks to 12 years of age is 160 mg/m^2 every 8 hours (480 mg/m^2/day up to a maximum of 200 mg every 8 hours) in combination with other antiretroviral agents.

Maternal-Fetal HIV Transmission
The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonates is:

Maternal Dosing
100 mg orally 5 times per day until the start of labor (see INDICATIONS AND USAGE: Description of Clinical Studies). During labor and delivery, intravenous zidovudine should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous intravenous infusion of 1 mg/kg/hour (total body weight) until clamping of the umbilical cord.

Neonatal Dosing
2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered zidovudine intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

Monitoring of Patients
Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

Dose Adjustment

Anemia
Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see WARNINGS). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance. For patients experiencing pronounced anemia while receiving chronic co-administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

End-Stage Renal Disease
In patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Hepatic Impairment
There are insufficient data to recommend dose adjustment of Ziodvudine in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since Ziodvudine is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients. Frequent monitoring for hematologic toxicities is advised (see CLINICAL PHARAMACOLOGY: Pharmacokinetic).
(SEE PRECAUTION:General).

HOW SUPPLIED
Ziodvudine oral solution, colorless to pale yellow strawberry flavored clear solution contains
50mg of Zidovudine in each 5mL in plastic bottles of 100 mL [NDC no 53104 0154 4] & 240 mL. [NDC no. 53104 0154 9]
Store at 20(C-25(C (68(F-77(F)[See USP Controlled Room Temperature].
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